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Academic–Industrial Collaboration: Toward the Consilience of Two Solitudes

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ABSTRACT: Current major advances in drug discovery can be traced back to pioneering contributions originating from academics over a century ago. Living in a symbiotic yet noninvasive coexistence, the academic community and the pharmaceutical industry have strived, each in their own way, to develop the modern medicines that benefit humankind today. The subject is presented from a historical and personal perspective.

KEYWORDS: *Natural products, targeted research, drug discovery, medicinal chemistry*

Human health and well-being has been the basic tenet of our existence as a people. Our history is replete with anecdotes of magic potions for a host of adverse physical conditions. Traditional folk medicines obtained principally from plant sources have long been used by many eastern cultures as remedies for a variety of conditions.[1] Quinine and morphine are still in clinical use centuries after their discovery. Already by the turn of the last century, "drugs" were considered to be the domain of the academic scientist who had synthesized urea, aspirin, amphetamines, and barbiturates, which eventually found their way to apothecaries that became some of today's multinational pharmaceutical companies.[2]

Monumental discoveries in academic institutions within the first half of the twentieth century saw the emergence of sulfa drugs, penicillin, and other anti-infectives, which proved crucial to combat bacterial infections and provide the first effective treatment of syphillis and tuberculosis. Vaccines against polio, diphtheria, Japanese encephalitis, among others, were used to keep such diseases and epidemics under control. Much of these discoveries became the foundation of the pharmaceutical industry in North America and Europe. For more than a century, the herculean efforts of the pharmaceutical industry to develop medicines have been of enormous benefit to the well-being of humankind.[3,4] Diseases that were deemed incurable only decades ago, can now be managed, if not conquered, largely due to the advent of modern drugs discovered in conjunction with tremendous advances in the biomedical field including genomics. Today, the drug industry is a multibillion dollar profit-based enterprise that continues to provide life-saving medicines to humankind.[5] However, as an industry, it is not immune to the trials and tribulations of financial fluctuations, to criticism regarding the high cost of drugs,[6] and the tendency of some companies to pursue research programs that are market driven rather than addressing some unmet medical needs toward diseases that may ultimately prove not to be profitable.

Advances in the biological and physical sciences principally in academia during the past 50 years have contributed immensely to our understanding of the molecular basis of many diseases. From deciphering the genetic code to the promised practice of personalized medicine, humankind finds itself in a privileged situation compared to only a few generations ago. Although tremendous strides have been made in the development of vaccines and so-called biologics as potential drugs, a large portion of the drug discovery and development process still relies on small molecules either produced by synthesis or derived from natural products.[7,8] It is clear that this practice will continue for the foreseeable future. Natural products have been the lifeline that has bridged the gap between academia and the pharma industry since its inception over a century ago.[7,9] Where academia and the pharma industry have common roots is in the significant number of marketed natural products or their chemically modified variants, which have traditionally been used mainly as antibiotics, anticancer agents, antivirals, and immunosuppresives to mention a few. The Nobel Prize for medicine or physiology for 2015 was shared by Satoshi Ōmura and William Campbell for the discovery of the anthelmintic agent avermectin B1a, and by Youyou Tu for the antimalarial artemisinin. Both natural products are used in their natural versions to treat river blindness and lymphatic filariasis and malarial infections, respectively, thus saving millions of lives. Although available by fermentation or other natural sources, the total synthesis and chemically modified variants of the life-saving natural products by academics has also shown ingenuity and resolve in the face of many obstacles. Many highly useful methodologies were also invented in the course of these studies.

Traditionally, the laboratory synthesis of drug substances has relied heavily on methodologies originally developed by academic organic chemists. Progress in this field has been phenomenal especially with the advent of sophisticated instrumentation and the invention of catalytic reactions in effecting various types of bond formation. In retrospect, the area of catalysis within academia has been inspired by seminal discoveries in the pharma industry. Monsanto's synthesis of the anti-Parkinson drug L-DOPA,[10] which rewarded W. S.

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Knowles, then a practicing chemist, to share the Nobel Prize in Chemistry in the year 2000, is a prime example of ingenuity that started a multitude of research programs in academia on metal-catalyzed enantioselective reactions, which continues to thrive to the present day across the broad domain of synthetic chemistry. A second example involves the proline-catalyzed intramolecular aldol reaction independently discovered by Hajos and Parrish at Hoffmann-La Roche company in Nutley, New Jersey,[11] and by Sauer, Wiechert, and Eder at the Sandoz company in Basel, Switzerland.[12] From these and related contributions has emerged the area of "organocatalysis" or "metal-free catalysis", which has gained enormous momentum in the last two decades.[13]

Many other innovative chemical technologies associated with drug development, particularly in process research,[14] have been invented in the pharma industry over the years even if much of it still remains locked behind closed doors, or encrypted in voluminous patents. Tactical decisions to heavily invest in techniques such as high throughput screening, combinational chemistry, molecular modeling, and *in silico* methods to accelerate the "hit rate" of potential drugs-to-be have had their share of successes and failures. More recently, the technique of "flow chemistry" appears to be making important strides in the quest of achieving efficiency toward "greener" laboratory practices.[15]

In spite of the tremendous advances in organic synthetic methodology in the academic community, including the ability to synthesize practically any molecular entity or complex natural product,[16] and a genuine desire to address biologically relevant problems through synthesis of analogues,[17,18] the pharma industry has remained an exclusive club that accepts academics "by invitation only". The most common form of interaction has been as consultantships and invitations to spend a day as guest speakers. In this respect, the host pharmaceutical scientists can benefit from recent innovative methodology developed in an academic laboratory. Clearly, the priorities in the two camps (and cultures) are different. Besides providing the best co-worker training possible, academics prioritize publication, aim for as much exposure of scholarly work as possible, seek sources of funding on a quasi-continuous basis, are open to collaboration, and strive to remain on good terms with the pharmaceutical industry. The main priorities of the pharma industry, however, consist in being first to reach the marketplace, to secure early patents to protect intellectual property, to maintain a position of prominence in the field, and to satisfy the shareholder's interests through sustained profits. The nature of relations with academia, while being cordial and supportive, may vary with the disciplines. High on the list are clinicians who provide valuable counsel in the translation of information from bedside to market. Traditionally, the pharma industry has recruited bench chemists with excellent laboratory practices and problem solving skills, knowing that the rest will be acquired "on the job". Once joining the ranks of a pharma company, they must put their academic achievements behind them, and rapidly adopt a different mindset that requires new rules of engagement and a paradigm shift toward teamwork across different disciplines. The learning curve that invariably involves interdisciplinary crosstalk for new recruits is steep and understanding the biology in order to engage in productive dialogue becomes a necessity. With the rapid evolution and tremendous advances in all aspects of the chemical and biological sciences, an academic synthetic organic chemist with adequate funding, has the opportunity to work in areas that bridge the gap between several disciplines. However, therein lies the dilemma in having to make the judicious selection of a project among several choices, based on a valid rationale, sound planning, and productive collaboration (if so desired), so as to have the highest impact in the foreseeable future. Clearly, even the best laid plans will not guarantee success. The Greek historian Thucydides is known to have proffered: "*How are we to divine the unseen future that lies hidden in the present?*" As academics, we are in an enviable position to be autonomous and to do the best science possible. However, we should also be cognizant of the changing times in the pharma industry and the rigors of drug discovery so as to educate our co-workers who want to become prospective medicinal chemists and to facilitate their rapid integration in the culture and practices of the industry. A restructuring of some graduate and undergraduate courses that better prepare students to deal with the translational nature of the drug discovery process and possibly future employment prospects would be a step in the right direction. In this regard, our colleagues in the pharma industry are also the best ambassadors of their own profession. Integrating them in our courses as guest lecturers would be of great benefit to the students and also to the speakers who are more than willing to share their experiences with prospective future recruits. Many pharma companies have training programs for students who get to see different aspects of "life in the fast lane". This practice could be expanded to stimulate better interactions with the academic community. Retired seasoned pharma scientists with a zest for research can also be integrated in University settings in various capacities.

How then can the two solitudes be reconciled in ways so as to engage in scholarly dialogue and share relevant non-proprietary information to the benefit of both parties with the ultimate aim of promoting the noble cause of drug discovery to meet the social and health needs of humankind? Many scholarly and valid opinions have been expressed over the years on the subject of academic−industry collaborations.[19−25] Much has also been written about the cyclical "good times" and "bad times" within the pharma industry.[26] Regrettably, terms such as "valley of death" referring to a difficult transition from first publication to market are somewhat disconcerting.[27]

My comments pertain specifically to the role of the academic *synthetic* medicinal chemist and to his or her involvement in this dialogue. As academic mentors and practitioners of the art of synthesis, we must continue to strive for the highest levels of chemoselectivity, stereoselectivity, and efficiency through the development of innovative chemistries. Our strength lies in our ability to invent new reactions that colleagues in the pharma industry can put to practice, and possibly improve in a process chemistry setting. As academics we can endeavor to produce "drug prototypes", but we should be weary of assuming the role of the pharma scientist who has all the amenities within the company to rapidly advance a project through various stages, then to potentially march it all the way to the market. In this age of the consilience of disciplines, some academic synthetic chemists have excelled at innovation and developed a flair for entrepreneurship in setting up their own startup companies with the help of investors, or through their own Universities. Many Universities have established academic screening centers to identify new active compounds within their internal resources or in collaboration.[22] According to a survey, it is estimated that among the 1453 FDA-approved new molecular entities, a significant number has had their origins in academic institutions particularly starting with the middle part of the

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twentieth century.[28] In this regard, we should salute the academic inventors of over a dozen presently marketed highly effective anticancer and antiviral drugs for their heroic efforts and successful partnerships with various pharmaceutical companies particularly based in the United States.[29−36]

There is ample room for collaborative projects between academia and the pharma industry, either directly with principal investigators or through established drug discovery centers within the institution possibly also involving government agencies[37] as well as benevolent foundations. Projects focusing on synthetic work could involve methods development, targeted syntheses of drug prototypes, and applications of reactions in specialized domains of the principal investigator. Academic laboratories can also be the source of unique compounds synthesized over the years and screened at pharma companies. My personal experience in this regard has been a highly successful one, having had multiple and simultaneous collaborative projects in my laboratory for more than 30 years, that continue to this day. Although this long lasting personal odyssey of industrial collaboration as an academic may be the exception rather than the norm, it begs the following question to be asked before embarking on such ventures: "How can we succeed in academic−industry collaborations, while keeping our chemical soul intact, being able to publish the results, and remain good friends with our pharma colleagues?" I humbly offer my suggestions for the creation of successful academic−industrial collaborations in the form of the "*Hanessian Rule of Five*": 1. Be involved and enthusiastic about the collaboration; 2. Develop and nurture mutual trust; 3. Learn and understand the biology; 4. Do what you say you'll do; 5. Give but do not to take (except for research support).

In an era of paradigm shifts within the pharma industry, increased regulatory restrictions, and a public outcry for access to cheaper and safer medicines, the overwhelmed academic chemist may decide to take a passive role and retreat in the traditional ivory tower of mentorship and to continue to do curiosity-driven research. Alternatively, we may choose the road less traveled and be willing to apply our knowledge as molecular architects of potential new drug substances to join hands with our colleagues in the pharma industry and to address the health issues of the future. To achieve such an objective, we need guidance, support, and sustained partnerships with the pharma industry while minimizing roadblocks from both sides. As synthetic chemists we can offer methodological knowhow that may be useful for further application toward a new drug entity. Reaching a fair balance between the value of what we offer and the prospects of reaching the market may have to endure and survive a treacherous path. It would be terribly unfortunate and potentially devastating if decisions to engage or not in collaborations remains in the hands of tech transfer offices and their legal counterparts in the companies. The initial phases of the drug discovery process is a labor intensive biology-based, chemically-driven endeavor, the outcome of which is difficult to predict. Academics must have realistic expectations of the significance of their discoveries and be careful to not overvalue their potential. There is an inherent difficulty to assess the future impact of a particular discovery without divulging sensitive information. Discussions in good faith possibly within the formal rules of material or information transfer agreements is normally a mutually acceptable practice. In most instances, the academics are the "solicitors" and the pharma industry the potential "providers". Reversing the scenario as in a David and Goliath story, although not without some precedent, is by and large an unrealistic academic utopian dream. Instead, let us work together to gain public trust and strengthen society's belief in the power of science by inventing the best medicines possible and ensuring the well-being of humankind for generations to come while we still can.[38,39]

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